Full Text AR-94-001

FAILURE TO HEAL: CHRONIC WOUND HEALING IN THE SKIN

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National Institute on Aging
National Institute of Child Health and Human Development
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National Institute of Nursing Research

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Application Receipt Date: November 30, 1993

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Aging (NIA), National Institute of Child Health and Human Development (NICHD), National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), and National Institute of Nursing Research (NINR) invite applications for research on wounds that fail to heal, the prototypic ones being decubitus (pressure) ulcers, venous (stasis) ulcers and diabetic ulcers. Studies may be both basic and applied. The intent is to apply knowledge rapidly to the prevention and treatment of chronic wounds in a clinical/rehabilitation situation.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), Failure to Heal: Pathogenesis of Chronic Wound Healing in the Skin, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Summary Report: Stock No. 017-001-00474-0 or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications from minority individuals and women are encouraged. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) (R29) award.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research grant (R01) and FIRST award (R29) and the newly described interactive R01 mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for applications submitted in response to the present RFA may not exceed five years. The anticipated award date is July 1, 1994. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will also vary. This RFA is a one time solicitation. Future unsolicitated competing continuation applications will compete with all investigator initiated applications and be reviewed according to the customary peer review procedures.

FUNDS AVAILABLE

The estimated funds (total costs) available for the first year of support for the entire program is anticipated to be 1.6 million dollars. The anticipated number of new awards is eight.

RESEARCH OBJECTIVES

Background

In spite of recent advances in the basic mechanisms of wound healing, knowledge of factors involved in the development and treatment of chronic wounds and their prevention remains limited. Future progress in the treatment of chronic wounds will require greater understanding of their pathogenesis and failure to heal. These two inseparable aspects, pathogenesis and failure to heal, were the subject of a Workshop sponsored by the Skin Diseases Interagency Coordinating Committee for the National Institutes of Health held on January 10th and 11, 1993. The Workshop brought together a multidisciplinary group of scientists working in the field of wound repair. A summary of this Workshop will be published in the Journal of Investigative Dermatology. Identified below is a selection of the areas covered in that workshop that are relevant to this solicitation. This list is illustrative and not exclusive or restrictive.

Cytokines and Growth Factors

A number of reports have established that the application of growth factors to acute experimental wounds in animals enhances healing. However, it is unclear what role growth factors play in chronic wounds. Indeed, recent clinical trials of topical application of single growth factors to pressure, venous and diabetic wounds have not been very encouraging. It should be appreciated that growth factors are multifunctional with both stimulatory and inhibitory actions depending upon cellular context. Among the areas of interest relative to cytokines and growth factors are:

o What is the normal sequence of growth factors in acute wounds and how are these altered in the chronic wound situation?

o Are growth factors being trapped by macromolecules present in chronic wounds?

o Are growth factors released by cultured cells, both allogeneic and autologous, that are applied to chronic wounds?

Keratinocyte Migration in the Wound Bed

In normal skin, the basal cells are attached to the basement membrane and lose anchorage upon skin injury. The signals responsible for epidermal migration after wounding are unknown, but keratinocytes begin to migrate toward the site of injury. The "tractor tread" hypothesis, whereby keratinocytes stop at the wound bed with progressive climbing of proximal cells over the now resting cells has gained wide acceptance as a model of keratinocyte migration. Investigations of the epidermal edge of venous ulcers has shown that the epidermis displays mitotic activity, resulting in increased epidermal thickness at the edges of chronic wounds. This has led to the

hypothesis that a fundamental defect exists in the chronic wound situation, perhaps a failure of cells to adhere to one another or their substrates. There has been substantial recent information on the signals for keratinocyte movement and substrate requirements at least in the context of acute injury. The concept that the extracellular matrix is an integral part of keratinocyte migration has also received experimental support. Migration enhancing and inhibiting molecules found in extracellular matrix and/or in wound beds have been described. Areas of research within this topic include:

o Investigations of specific cytokine and growth factor actions in relation to keratinoctye migration;

o Specific elucidation of the stimulatory and/or inhibitory effects of the extracellular matrix molecules on keratinocyte migration;

o Specific investigation of the basis for the failure of keratinocytes to migrate across the bed of chronic wounds.

The Chronic Wound Environment

For the last several years, evidence has suggested that chronic wounds may be growth factor deficient or represent a microenvironment hostile to the repair process. More recently, however, there is new evidence suggesting that wounds may not necessarily be deficient in growth factors, but that the stimulatory action of the peptides may be prevented from being expressed. Areas of inquiry in this subject include:

o Investigations of wound fluids from acute and chronic wounds to establish whether or not there is a difference in regard to stimulation and/or inhibition of the wound healing process;

o Investigations designed to determine whether or not macromolecules present in the chronic wound bed act as a trap for endogenous growth factors, making them unavailable to the maintenance of tissue integrity and the repair process at the wound site.

Matrix Degrading Metalloproteinases

Matrix degrading proteinases are proenzymes that need to be activated and are considered to be the physiologic mediators of matrix degradation. The prototypic one is interstitial collagenase, but there are at least ten of these enzymes that are secreted as zymogens. Stimulated by growth

factors and by extracellular matrix, they all utilize zinc with a zinc atom binding at the center of the molecule at a conserved sequence. They are stabilized by calcium and inhibited by various chelators such as the tissue inhibitor of metalloproteinase. It is clear that collagenases are present in acute wounds, but little or nothing is known about their possible role in chronic wounds. Within this area, research topics might include:

o Investigations of the source of metalloproteinases in acute and chronic wounds;

o Identification of which members of the metalloproteinase family are present and in what sequence in both acute and chronic wounds;

o Investigations of the role of the inhibitors of the metalloproteinases in the wound healing process.

Metabolic Abnormalities

The incidence of chronic wounds appears to be higher in persons suffering from disease conditions such as diabetes or physical disabilities due to mobility impairments such as those that result from spinal cord injury (SCI). Little is known about how changes in the homeostatic mechanisms of persons having either of these conditions predispose them to wounds, or how they affect wound repair. Though the categories of chronic wounds that are prevalent in both conditions vary, there may be similar etiologies. For diabetic wounds, both neurological abnormalities and vasculopathy have been postulated in explaining the pathogenesis of the diabetic ulcer. In persons with SCI, changes in sensory innervation and circulation provide a spectrum of metabolic changes that can predispose to the development of chronic wounds.

In this area, further research could include:

o Investigations of small vessel abnormalities as a contributor to diabetic ulceration;

o Investigations of the effect of neurotransmitters and neuropeptides for their effect upon the inflammatory and wound healing process;

o Investigations of the effects of excess glucose or sorbitol on cell metabolism in the context of wound repair.

Hypoxia

Oxygen plays a major role in wound repair and probably is a fundamental aspect of chronic wound pathogenesis. For the most part, the biology of oxygen in wound healing has been studied in the context of connective tissue synthesis. Oxygen also has important effects on a number of enzyme systems that can alter cell behavior. In this subject area, further investigation would be possible in:

o Effect of oxygen or lactate in the stimulation of extracellular matrix and/or in the fibrotic reaction observed in some chronic wounds;

o The interaction of low oxygen tension with the release of various growth factors and cytokines and their effect on the wound healing process.

Fibrin Formation and Removal

Chronic wounds, including pressure ulcers and venous ulcers, are characterized by the presence of fibrin within the wound bed and surrounding tissues. Fibrin accumulation in acute wounds is removed within days, but it is not degraded in chronic wounds. Knowledge of the process of fibrin formation and polymerization that has accumulated in recent years may provide the basis for understanding the persistence of fibrin in chronic wounds. The role of fibrin retention and the adherence of other molecules to it in interacting with cytokines and growth factors in the wound healing process have just begun to be investigated. In this area, new research approaches could include:

o Investigations of the process of fibrin accumulation in chronic wounds;

o Investigations of specific macromolecules that bind to fibrin in the chronic wound bed and their influence on wound healing;

o Investigations of the fibrin polymers seen in chronic wounds and their comparison to that seen in acute wounds.

Aging and Chronic Wound Healing

It has been noted by many investigators that wound healing is slower in older individuals, but the underlying cause and mechanism is not understood. Areas of interest include:

o Changes in composition of extracellular matrix with advancing age;

o Alterations in wound healing with advancing age.

Clinical Therapeutics

An important focus of wound healing research is the improvement of patient care through the interdisciplinary collaboration between clinicians and basic scientists. Restoration of physical integrity and function of the injured or diseased tissue can best be accomplished by integrating bio/molecular technology with clinical treatments as clinicians and basic scientists work together. Examples to encourage opportunities for clinicians to collaborate with basic scientists include:

o Investigations designed to determine the biological or molecular reason for successful wound healing with currently used clinical therapies, such as electrical stimulation, laser, or nutritional regimens. For example, clinicians have reported faster healing of pressure sores with patients on high protein diets. In order to identify the pivotal amino acid, methionine, cysteine, or arginine might be studied. Because zinc is a necessary cofactor of DNA polymerase and reverse transcriptase, studies could be pursued to determine whether or not the healing impairment associated with zinc deficiency is due to an inhibition of cellular proliferation

o Investigations designed to identify specific biological/molecular markers that could be used to define standardized outcome measures. For example, various dressings such as hydrocolloid, polyvinyldiene, polyethylene, polyurethane, and human skin are used in health care facilities to increase the rate of epithelial healing. Can serum protease inhibitors or tissue inhibitors be identified in the fluid of chronic wounds to standardize use of specific wound cleansers and dressings in the treatment of pressure sores/venous leg ulcers?

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to

males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues must be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 (rev. 9/91) in Sections 1-4 of the Research Plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans [including American Indians or Alaskan Natives], Asian/Pacific Islanders, Blacks, Hispanics).

The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including, but not limited to, clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population

is inadequate, it will be considered a scientific weakness or deficiency in the study design and reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

GENERAL CLINICAL RESEARCH CENTERS

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or Principal Investigator could be included with the application.

LETTER OF INTENT

Prospective applicants are asked to submit, by October 15, 1993, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows ICD staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to Dr. Alan N. Moshell at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research; from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone 301/435-0714.

The RFA label available in the PHS 398 (rev. 9/91) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the

RFA title and number must be typed on line 2a of the face page of the application form and the YES box must be marked.

Applications for the FIRST Award (R29) must include at least three sealed letters of reference attached to the face page of the original application. FIRST Award (R29) applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two additional copies of the application must also be sent to Dr. Alan N. Moshell at the address listed under INQUIRIES.

Applications must be received by November 30, 1993. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this announcement that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the DRG and responsiveness by the NIAMS. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, ICD staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications may be triaged by an ICD peer review group on the basis of relative competitiveness. The NIH will withdraw from further competition those applications judged to be

non-competitive for award and notify the applicant Principal Investigator and institutional official. Those applications judged to be competitive will undergo further scientific merit review. Those applications that are complete and responsive will be evaluated in accordance with the criteria stated below for scientific/technical merit by an appropriate peer review group convened by NIAMS. The second level of review will be provided by the National Advisory ICD Council/Board.

Review criteria for this RFA are generally the same as those for unsolicited research grant applications and include:

o scientific, technical, or clinical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research;

o responsiveness to the RFA objectives.

AWARD CRITERIA

The anticipated date of award is July 1, 1994.

Awards will be based upon the following criteria:

o priority score
o availability of funds
o programmatic priorities of the funding ICD
o responsiveness to the RFA

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged.

The opportunity to clarify any issues or questions from potential applicants is welcome.

Address the letter of intent and send two copies of the completed application to:

Alan N. Moshell, M.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 752
Bethesda, MD 20892
Telephone: (301) 594-9955
FAX: (301) 594-9673

Direct inquiries regarding programmatic issues to:

Hilary D. Sigmon, Ph.D., R.N.

National Institute for Nursing Research
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 594-7397
FAX: (301) 594-7603

Dr. David Finkelstein
National Institute on Aging
Gateway Building, Room 2C231
Bethesda, MD 20892
Telephone: (301) 496-6402
FAX: (301) 402-0010

Dr. Danuta Krotoski
National Center for Medical Rehabilitation Research
National Institute of Child Health and Human Development
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Dr. Charles A. Wells

National Institute of Diabetes and Digestive and Kidney Diseases
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Telephone: (301) 594-7505
FAX: (301) 594-9011

Direct inquiries regarding fiscal matters to:

Mary Graham
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Betty E. Bailey
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National Institute of Diabetes and Digestive and Kidney Diseases
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FAX: (301) 594-7594

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.361. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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